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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,571	12/27/2001	Shuyuan Zhang	29853/37702	9714

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	

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02/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/033,571	ZHANG ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 31, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-72,74-77,79-128 and 130-162* is/are pending in the application.

4a) Of the above claim(s) *99-128* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-72,74-77,79-98 and 130-162* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :3/26/07,10/31/07,12/12/07&2/14/08.

DETAILED ACTION

The Office action mailed February 5, 2008 is VACATED in favor of the following Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Claims 70-72, 74-77, 79-98, 130-162 are examined on the merits. Claims 99-128 are withdrawn from consideration since they are drawn to a non-elected invention stemming from the Office action of June 22, 2004.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on March 26, October 31 and December 12, 2007 and February 14, 2008 were filed after the mailing date of the Final Rejection on March 16, 2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/031,329, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. There is no mention of serum-free media usage in the disclosure of '329. Therefore, claims 79 and 140 will be given the priority date of November 20, 1997.

Declarations Under 37 C.F.R. 1.132

The declarations under 37 CFR 1.132 filed October 31, 2007 by Peter Clarke, Ph.D. and Shuyuan Zhang, Ph.D. are insufficient to overcome the rejection of claims 70-72, 74-77, 79-98 and 129-162 because the arguments made are pertaining to effectiveness of Benzonase® to efficiently degrade nucleic acids at low pH, that treating cell lysates by ultracentrifugation resulted in Benzonase® treatment of only viral supernatants and not cell lysates, therefore, the level of contamination was initially lower than if cell lysates are included. Furthermore, these declarations also argue that adenovirus protein expression systems do not correlate with virus yield and that the teachings of the referenced material do not discuss how to enhance adenovirus production by altering cellular conditions. In response, none of the cited references discuss the low pH that applicants claim inhibits Benzonase® activity and even though centrifugation is

used by Sastry et al. the claimed invention does not exclude such a step in purifying viral preparations, it only excludes the use of cesium-chloride gradients and the method states that it "comprises steps", not "consists of steps". Furthermore, Nadeau et al. is referenced to show that maintaining glucose levels after viral infection and limiting the amount of lactate build-up results in the highest protein expression from the recombinant adenovirus vector and even though Nadeau et al. focus on recombinant protein production, the adenovirus vector used would inherently replicate in the host cells of 293A since these cells constitutively express the E1A and E1B genes of adenovirus and therefore operate in *trans* to support viral replication. This *trans* activity would therefore produce viral progeny at the same time as recombinant proteins during the high volume cultures of Nadeau et al.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Claim Objections

Claims 71, 72, 74-77, 79-98 and 130-132 are objected to because of the following informalities: these ultimately depend from claim 129 which is cancelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71, 72, 74-77, 79-98 and 130-132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 71, 72, 74-77, 79-82, 88, 92-94, 97, 98 and 130-132 recite the limitation "claim 129" in line 1. There is insufficient antecedent basis for

this limitation in the claim. Claims 83-91, 95 and 96 are rejected since they depend from some of the rejected claims above.

Response to Arguments

Applicant's arguments filed October 31, 2007 have been fully considered but they are not persuasive. See responses below.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 70 and 133-162 are rejected under 35 U.S.C. 103(a) as being obvious over Shabram et al. (US 5,837,520), Huyghe et al. (Human Gene Therapy, 1995), Kozak et al. (Developments in Biological Standardization, 1996), Keay et al. (Biotechnology and Bioengineering, 1976), Nadeau et al. (Biotechnology and Bioengineering, 1996) and Griffiths J.P. (Animal Cell Biotechnology, 1986).

One of the applied references has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in

the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Applicants argue that Shabram et al. do not teach the specific levels of contaminating nucleic acids either inherently or explicitly. In response, the examiner acknowledged that Shabram et al. did not explicitly state that these low contamination levels were achieved, however, the primary active step which removes contaminating nucleic acids is the same between Shabram et al. and the instant invention (i.e., Benzonase treatment) as evidenced by Sastry et al. (Human Gene Therapy, 2004), while adding additional steps in processing, Sastry et al. still incubated their viral preparation under the same conditions as in the instant invention, and (Sample Preparation Tools for protein Research, 2nd Edition, 2006) which depicts efficient degradation of nucleic acids on page 54- see bottom figures.

Applicants argue that Huyghe et al. teach the use of steps that are excluded by the instant invention (i.e., cesium chloride purification). In response, this is not disputed that Huyghe et al. relies on cesium chloride in the initial purification step. However, it is the additional column chromatography steps of Huyghe et al. that achieve the highest particles to pfu ratios, while the cesium chloride step merely serves to remove cellular fragments. Furthermore, the open claim language of claim 70 does not exclude additional steps.

Applicants argue that Kozak et al. and Keay et al. do not teach any of the contaminating nucleic acid levels or BSA levels following purification. In response, it is acknowledged that neither Kozak et al. nor Keay et al. teach the reduced levels of contaminating BSA or nucleic

acids. However, based on the concern of BSE elements in bovine products with regard to producing pharmaceutical compositions as taught by Kozak et al. and the successful propagation of adenoviruses in serum-free media as taught by Keay et al., one skilled in the art would be motivated to adapt their viral production method to eliminate serum from growth media.

Applicant argue that Nadeau et al. do not teach adenovirus production and that they actually teach away from using fed-batch processes in culturing cells with adenovirus vectors. In response, Nadeau et al. reports in table 1 that changing media at the time of infection results in the lowest protein yield being obtained. This could suggest to not use fed-batch systems when infecting cells. However, the claimed invention only requires that nutrients are provided to host cells by perfusion or through a fed-batch process, nothing is claimed that requires media exchange during or after infection. Furthermore, figure 8 depicts the highest protein production resulting from Nadeau et al. maintaining glucose levels and removing lactate before and after infection.

Applicants argue that Griffiths is not relevant to the present rejection. In response, the examiner believes the teachings of Griffiths expose the importance of optimizing large scale tissue culture systems by employing micro carriers for attachment dependent cells since Shabram et al. use the attachment version of HEK 293 cells.

Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin P. Blumel whose telephone number is 571-272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin P Blumel/
Examiner
Art Unit 1648

/Bruce Campell/

Supervisory Patent Examiner, Art Unit 1648